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OBLON, SPIVAK, MCCLELLAND, MAIER & NEUSTADT, P.C.
1940 DUKE STREET
ALEXANDRIA, VA 22314

EXAMINER	
KAPUSHOC, STEPHEN THOMAS	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 10/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/714,852	SENPUKU ET AL.	
	Examiner	Art Unit	
	Stephen Kapushoc	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 2* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 2* is/are rejected.

7)☒ Claim(s) *2* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 November 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Specification

1. The disclosure is objected to because of the following informalities: the specification contains typographical errors. For example page 8 line 8 contains the word 'ast', where it is assumed applicant intends to use the word 'as'.

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Objections

2. Claim 2 is objected to because of the following informalities: as written the claim contains a period before the end of the claim, and also no period at the end of the claim. MPEP 608.01(m) describes the Form of Claims: Each claim begins with a capital letter and ends with a period. Periods may not be used elsewhere in the claims except for abbreviations. Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1 and 2 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are generally narrative and indefinite, failing to conform with current U.S. practice. They appear to be a literal translation into English from a foreign document and are replete with grammatical and idiomatic errors. For example, the phrase 'indentifying a genotype of DRB1* in a class II type of a HLA gene group' should be corrected to more properly convey the gene of applicant's interest. The phrase could be changed to read 'identifying a subject's genotype for the DRB1 gene, said gene being in the HLA class II gene group'.

Claim 1 is vague and indefinite in the recitation 'a method for examining the caries risk' in the preamble of the claim. The claim does not include how the caries risk is in fact detected, hence the single method step does not correlate with the preamble and it is unclear how the claimed method accomplishes the purpose of the method.

Claim 2 is vague and indefinite in the recitation of identifying the DRB1* genotype 'according to claim 1'. Claim 1 provides no guidance regarding how to identify the DRB1* genotype, it only states 'identifying a genotype of DRB1*'.

Claim 2 is vague and indefinite in the recitation of 'which is identified beforehand'. It is unclear if applicant intends to mean that genotypes which correlate to high antibody values have been previously determined, or if the antibody value of the particular individual under study has been previously determined.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1 and 2 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification does not provide for a method in which the caries risk can be determined through the identification of the genotype of DRB1* in a class II type of a HLA gene group.

Nature of the Invention and Breadth of the Claims

Claims 1 and 2 are drawn to methods for determining the caries risk in an individual. The methods comprise identifying the genotype of DRB1 in a class II type of a HLA gene group, and in the case of claim 2 comparing the genotype with a previously determined caries risk as determined by an anti-PAc antigen antibody value.

Claim 1 encompasses identifying the caries risk in any animal subject, and also includes the analysis of any possible DRB1 genotype as it may be indicative of increased or decreased caries risk. Claim 2 additionally includes any method in which the antibody value of a secretory immunoglobulin A from saliva in humans is determined using SEQ ID NO: 1 as an antigen, and comparing this antibody value to the identified genotype.

The nature of the invention requires knowledge of the correlation between the caries risk of an individual and DRB1 genotype.

State of the Prior Art, Level of Skill, and Level of Unpredictability

The prior art concerning to the investigation of HLA-DRB1 genotypes and phenotype teaches the examination of particular genotypes with regard to several diseases that involve immune system components. Though the level of skill with regard to identification of different HLA-DRB1 genotypes in humans is high, results from attempts to demonstrate an association between any particular genotype and a disease state are indicative of an even higher level of unpredictability. Some of the unpredictability in correlating HLA-DRB1 genotype to disease predisposition is due to the highly polymorphic nature of the gene. Epplen et al (1997a) teaches the extremely polymorphic nature of HLA-DRB1, and indicates that DRB1 is the most polymorphic protein-coding locus in man and all vertebrates (p.399 – Abstract).

Acton et al (1999) and Ozawa et al (2001) teach the determination of an association between MHC alleles and the caries risk. Acton et al teaches the association of DRB1*3 and DRB1*4 with caries risk (as determined by high levels of S. mutans and development of caries) (p.986, right column, l.45); and Ozawa et al teaches the association of DRB1*802 and DRB1*1302 with caries risk (as determined by high oral levels of lactobacilli) (p.355, right column, l.11). While these prior art references may be enabling for the practice of the claimed invention with regard to these specific alleles in the particular populations that were studied, the specification of the instant application cannot be considered enabling for these embodiments because they are not described in the specification. Additionally, both Acton et al and Ozawa et al exemplify the unpredictable nature of this art: Acton et al was not able to show an association between any other DRB1 alleles and caries risk, and Ozawa et al was not able to show

an association between any other DRB1 allele and high levels of lactobacilli or an association of any DRB1 allele with high levels of S. mutans.

Epplen et al (1997b) teaches the analysis of HLA-DRB1 genotypes in attempts to determine predisposition to multiple sclerosis (MS), early onset pauciarticular arthritis (EOPA) and rheumatoid arthritis (RA). The reference teaches the complex nature of using HLA-DRB1 genotypes as indicators of disease predisposition, and shows that it is often necessary to examine other genetic factors in addition to HLA-DRB1 genotype (Fig4; p.1583 – HLA and disease association: functional aspects vs. linkage disequilibrium). In the examination of MS predisposition, the reference teaches the analysis of more than 600 MS patients and the respective number of controls (p.1582, right column, l.21). The reference further teaches that while DRB*15 correlates with an increased risk of MS, the increased risk of DRB1*03 individuals is hardly recognizable (p.1582, right column, l.31). However, when the DRB1*03 allele is found together with a certain allele of another gene (TCRBV6S3), the risk of developing MS increases 22-fold (p.1583, left column, l.1).

Wyand et al (2000) teaches the use of HLA-DRB1 alleles as predictive indicators of RA. The reference indicates that different alleles (alone and in combination) have been associated with different forms of the disease (p.214, left column, l.7); but the reference also indicates that showing an association between an allele and a phenotype is not necessarily a sign of the extent to which a polymorphism can can be used as a biomarker to predict disease course (p.214, left column, l.20). The reference further teaches that proper analysis of the association between HLA allele and disease

requires sufficient patient numbers to control for disease and treatment variables, and to assess the impact of polymorphisms and gene dosing (p.214, left column, l.21).

Walkyria et al (2001) teaches the analysis of HLA alleles with regard to type 1 diabetes in a Brazilian population. The study concludes that there are several haplotypes which include specific DRB1 alleles that occur with increased frequencies in patient groups, as well as a particular DRB1 genotype which correlated to the highest risk for type I diabetes (p.1226 – Abstract). To reach these conclusions, the study utilized a case-control analysis of 181 individuals, which included 70 patients and 111 healthy subjects, in which multiple genes were simultaneously analyzed (p.1227 – Subjects, HLA typing). The conclusion that DRB1*03 and DRB1*04 alleles are indicators of type 1 diabetes susceptibility are drawn from the statistical analysis of the occurrence of these alleles in multiple patients versus controls (p.1229 – predisposing and protective alleles; p.1230 – Table 2). However, pointing to the unpredictability of the utility of DRB1*401 as a susceptibility marker, the reference teaches that the effect of DRB1*401 is variable depending on the population studied (p.1231, left column, l.14). The reference also points out the unpredictability of the effect of different alleles in different populations when teaching the lack of a protective effect of a haplotype that includes DRB1*1501 in the Brazilian population, indicating that such a haplotype usually confers a dominant protective effect in most populations; and that although the population under study was small, the DRB1*1501-containing haplotype was found in two diabetic patients (p.1232, left column, l.5).

Collectively, these studies teach the requirements that enable the determination of an association between a DRB1 allele and a phenotype. Such a determination requires a case-control study with a population large enough to allow a statistically significant analysis of the data. The studies also show the importance of examining other genes (e.g. establishing haplotypes) when investigating DRB1-phenotype associations. Importantly, the studies show that given the enormous number of DRB1 alleles, not every allele will be predictive. Determining an association requires finding a particular allele multiple times in affected or control subjects, and it is a preponderance of alleles in a particular group, not just a single instance of an allele in a single subject, which serves as the basis of the determination.

Amount of Direction Provided and Working Examples

The instant application provides no working example of the use of the claimed method for examination of the caries risk. Furthermore, the specification does not provide any analysis or evidence suggesting a reliable predictive relationship between HLA DRB1 alleles and caries risk. As noted previously in the rejection, knowledge of such a relationship is essential for the practice of the claimed invention.

The specification of the instant application provides an example (p.13 – Example 1) in which DRB1* genotypes and anti-PAC antibodies were analyzed. The specification teaches the determination of HLA-DRB1 genotype via a PCR-RFLP method. The specification teaches the use of several primers (p14-15) for DRB1 amplification:

Primers	Alleles amplified
DR3 and AmpB	DRB1*03, 08, 11, 12, 13, 14
DR4-like and AmpB	DRB1*1122, 1410, 1130

The specification does not specifically describe the use of any other primers for the amplification of any other HLA-DRB1 alleles. The specification further describes the treatment of the amplified DRB1 fragments with restriction enzymes, but does not indicate what type of restriction pattern is indicative of any particular genotype.

The specification also teaches the measurement of secretory anti-PAc antibodies in human saliva. The specification teaches an ELISA assay (p.17) in which a PAc peptide, corresponding to amino acids 361-386 of the S. mutans PAc protein, is used as an antigen, and alkaline phosphatase-labeled anti-human IgA is used to detect to detect anti-PAc antibodies. The specification teaches that a high level of anti-PAc antibodies is indicative of a low caries risk (p.11 l.4).

The specification teaches the comparison of HLA-DRB1 genotypes and anti-PAc antibody levels in the saliva of five individuals (p.20 and Table 1). However, the specification teaches that the five individuals (each of which were placed into one of two groups: High antibody value and Low antibody value) all have unique DRB1 alleles. There is no statistical analysis of the data, and in fact the results indicate that no particular genotype is found in more than one individual within either the High versus Low antibody groups, or within the entire population studied; there is no repeated finding of any particular genotype that would lead one to believe that such a genotype would indicated a predisposition or susceptibility for developing caries. In fact, the example provided in the instant specification does not indicate there exists any correlation between any HLA-DRB1 genotype and antibody levels or caries risk. Furthermore, there is no validation of the predictive use of DRB1 genotypes in

examining caries risk, nor any analysis of whether or not the individuals in the study actually developed caries.

Quantity of Experimentation Needed to Use the Invention

The quantity of experimentation required to use the claimed invention is high. If one wished to use the methods outlined in the instant specification to determine caries risk, one would first have to conduct a larger scale case-control study to discover which DRB1 alleles are present in caries-sensitive subjects versus subjects resistant to caries. Such a study may be focused on a general population or a specific subpopulation (e.g.: ethnic or geographic), and may also include corrections for environmental factors such as diet or hygiene. Such a study would have to be large enough in scope to detect correlations between any of the many different DRB1 alleles and a risk of caries; as the specification indicates, solving all combinations of DRB1 dimers would allow for accurate evaluation of the caries risk (though the instant specification provides information about DRB1 alleles from only five individuals). Validation of any specific alleles alleged to be useful for prediction of an increased caries risk would have to go beyond just showing a correlation with increased antibodies or higher levels of S. mutans in the oral cavity, and have to show an actual correlation with increased caries development.

Conclusion

Taking into consideration the factors outlined above, including the nature of the invention and scope of the claims, the state of the art and its high level of unpredictability, the lack of guidance by the applicant and the lack of a working

example, it is the conclusion the an undue amount of experimentation would be required to use the invention as claimed.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Ozawa et al (2001).

Ozawa et al teaches a method with the characteristic of identifying the genotype of DRB1 (p.354 – HLA typing). Ozawa et al teaches an investigation into the genetic predisposition toward the accumulation of oral microorganisms, including showing an association between alleles of HLA-DRB1 and the salivary numbers of lactobacilli. The reference teaches the analysis of salivary counts of lactobacilli from the subjects of the study, and the placement of the subjects into one of two groups: those having high numbers of microorganisms in saliva samples, and those having low numbers of microorganisms in saliva samples (p.354 – Table 1). The reference further teaches the determination of HLA genotypes in the subjects of the study (p.354 – HLA typing). Ozawa et al teaches an association between DRB1*0802 and *1302 and high numbers of lactobacilli. Ozawa et al concludes that the data suggest that HLA class II alleles may be related to the salivary populations of oral microorganisms (p.356, last

paragraph), and also teaches that there is an association between dental caries and salivary numbers of lactobacilli, thus indicating that identifying HLA alleles is useful for examining the caries risk (p.355 – Discussion).

9. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Acton et al (1999).

Acton et al teaches a study comparing the levels of cariogenic bacteria between those with and without a particular MHC allele (p.985 – Study design). As required by claim 1, the reference teaches the genotyping analysis of HLA-DRB1 in the subjects (p.986 – Genetic analysis). The oral bacterial profile of each subject of the study was also examined (at two time points) by measuring the number of colony forming units per milliliter of stimulated saliva (p.985 – Bacterial profiles). The reference further teaches management of the data to account for use of antibiotics by the subjects which affected bacterial levels (p.986 – Statistical analysis). Acton et al teaches an analysis of the results of bacterial profiling as related to DRB1 allele genotype (Table 1). The reference teaches that of the subjects who possessed a DRB1*3 allele, a statistically significant larger proportion had high levels (66%) compared with low levels (34%) of S. mutans (p986 – Results), thus concluding that identifying HLA alleles is useful for examining the caries risk.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 1 and 2 are rejected under 35 U.S.C. 103(a) as being unpatentable over Acton et al (1999) in view of Matsushita et al (1994) and Senpuku et al (1998).

Claim 1 is drawn to a method for examining the caries risk by identification of HLA-DRB1 genotype in a subject. Claim 2 creates the further limitation that the caries risk is identified beforehand by analyzing secretory immunoglobulin A in human saliva using an antigen that contains the amino acids of SEQ ID NO: 1 (corresponding to amino acids 361-386 in the S. mutans PAc protein).

Acton et al teaches a study comparing the levels of cariogenic bacteria between those with and without a particular MHC allele (p.985 – Study design). As required by claim 1, the reference teaches the genotyping analysis of HLA-DRB1 in the subjects (p.986 – Genetic analysis). The oral bacterial profile of each subject of the study was also examined (at two time points) by measuring the number of colony forming units per milliliter of stimulated saliva (p.985 – Bacterial profiles). The reference further teaches management of the data to account for use of antibiotics by the subjects which affected bacterial levels (p.986 – Statistical analysis). Acton et al teaches an analysis of the results of bacterial profiling as related to DRB1 allele genotype (Table 1). The reference teaches that of the subjects who possessed a DRB1*3 allele, a statistically significant larger proportion had high levels (66%) compared with low levels (34%) of S. mutans

(p986 – Results), thus concluding that identifying HLA alleles is useful for examining the caries risk.

Acton et al does not teach the prior identification of the caries risk using an analysis of salivary antibodies utilizing an antigen with SEQ ID NO: 1.

Matsushita et al teaches the detection of anti-PAc antibodies using synthetic peptide antigens as a diagnostic test for caries risk, and demonstrates the use of ELISA analysis of anti-PAc antibodies in human saliva (p.4035 – ELISA; p.4037 – Fig. 2B). The reference also teaches the use of synthetic peptides to map the continuous antigenic epitopes of the PAc protein, including peptides covering the A-region, which includes amino acids 361-386. Furthermore, Matsushita et al teaches a highly antigenic epitope in the A2-A3 junction of the A region (which includes amino acids 361-386) in the analysis of saliva from 5 different human subjects (p.4038 – Fig.4).

Senpuku et al teaches a detailed analysis of the PAc protein sequence to identify A-region antigenic peptides that bind to HLA-DR molecules, using a panel of overlapping synthetic peptides. The results from the analysis of DRB1 binding to various peptides indicates the strong binding of HLA-DR molecules to several relevant peptides, including PAc(369-387) and PAc(361-379), which bound strongly to molecules in four out of nine and three out of nine subjects, respectively (p.326, left column, l.29; Table 2).

It would have been prima facie obvious to one of skill in the art to have modified the method of Acton et al to include the antibody based method of Matsushita et al to determine the caries risk of an individual. One would have been motivated to do so in

order to provide an alternate means of detecting an increased caries risk, and based on the assertion of Matsushita et al that detection of anti-PAc antibodies in saliva using synthetic peptides as antigens is useful in development of a diagnostic test for dental caries (p.4040, last paragraph of discussion). One would have had a reasonable expectation of success because Matsushita et al demonstrates successful results in several individuals, and indicates that epitope patterns among the subjects examined were similar to each other (p.4038, last sentence). Claim 2 creates the limitation of using an antigen that is 'composed of' SEQ ID NO: 1, which leaves the claim open to the inclusion of an antigen that contains additional amino acids. It would have been prima facie obvious to use a synthetic peptide antigen that includes the amino acids of SEQ ID NO: 1 (PAc 361-386) by combining the peptides PAc(355-373) and PAc(369-387) (as described by Senpuku et al) to take advantage of the antigenic components of each peptide. One would have been motivated to use such a peptide because Matsushita teaches the successful use of such peptides as antigens (p.4036 – Epitope scanning of the PAc molecule; Fig. 4), and Senpuku et al teaches the high reactivity of HLA-DR molecules with these (Table 2).

Conclusion

12. No claim is allowed

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-

272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached at 571-272-0745. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen Kapushoc
Art Unit 1634

JULIET C. SWITZER
PRIMARY EXAMINER